Eosinophilic esophagitis caused by grass pollen sublingual immunotherapy with tolerance to a subcutaneous extract

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Eosinophilic esophagitis (EoE) is an immune-mediated chronic esophageal disorder characterized by symptoms of esophageal dysfunction and a predominantly eosinophilic inflammation with >15 eosinophils per high power field. It is due to a type 2 cell-mediated immune response mainly driven to food allergens.

EoE may develop during oral food immunotherapy in patients with IgE mediated food allergy, affecting between 2.7 to 5.7% of patients undergoing oral tolerance induction to milk, egg or peanut [1]. Apart from food, the involvement of airborne allergens in EoE has been less frequently confirmed. Moreover, the relation between EoE and sublingual immunotherapy (SLIT) has been scarcely described in the literature.

A 39-year-old female was referred to our allergy unit in September 2014 with a history of 10 years of seasonal rhinoconjunctivitis and mild allergic asthma due to grass pollen sensitization. She referred oculonasal symptoms in spite of daily antihistamines as well as daily cough, wheezing and mild dyspnoea. One-year prior preseason (January to March) SLIT with a standardized grass mix and *Cynodon dactylon* pollen extract (Sublingual Spray Maxi®, Diater SA, Leganés, Spain) was started. She had no history of food allergy.

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She also suffered for over 20 years from recurring digestive symptoms consisting in nausea, heartburn, and burning stomach pain. At the age of 18, a peptic esophagitis and chronic gastritis was diagnosed by esophago-gastro-duodenoscopy (EGD) and she was treated with proton pump inhibitors (PPI) at that time. She also underwent *Helicobacter pylori* eradication with improvement of her symptoms, although some heartburn persisted occasionally. No esophageal biopsies were taken at that time. Nonetheless, in January 2014 an abrupt worsening of her previous digestive symptoms led her to a new EGD in March that revealed erythematous mucosa in distal esophagus. An esophageal biopsy showed >25 eosinophils per high-power field. She was treated with poly-enzymes, dimethicone, succinate and metoclopramide with progressive improvement.

After a meticulous clinical history, we established the timeline of patient's symptoms linking the relapse to the initiation of the second season of SLIT and the resolution to SLIT finalization. A new EGD was carried out in December 2014 revealing the complete remission of the disease, with no signs of local inflammation nor the presence of eosinophils in esophageal biopsies. The patient was not taking PPI or corticosteroids at that time.

On the other hand, seasonal respiratory symptoms improved after 2 years of SLIT and the patient asked to continue pollen immunotherapy. Sensitization to grass pollen was confirmed by prick test and specific IgE (rPhl p 1 and 5 of 63 kU/L, total IgE of 114 kU/L). Allergy tests were negative to foods. Subcutaneous immunotherapy (SCIT) with a grass pollen extract (Depigoid®, Leti Pharma, Madrid, Spain) was initiated and she completed 5 years of treatment with a favourable response. The bronchial symptomatology ceased and rhinoconjunctival symptoms kept mild requiring antihistamine exceptionally. Seldom digestive indisposition responded to on demand PPI regimen in a satisfactory manner. The follow-up EGD in December 2017, after 3 years of SLIT and without taking PPI, confirmed full remission of the EoE, with persistent antral gastritis.

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We report a case of a woman that developed EoE caused by a grass pollen sublingual extract. The cause-effect relationship was supported by chronological correlation with both clinical symptoms and endoscopic/histologic findings. Apart from the well-established role of food antigens in EoE, the involvement of inhaled airborne allergens in an inflammatory response in the lung and esophagus has been proved in murine models [2]. Some studies established a connection between pollinic season and the display of EoE symptoms and diagnosis but a systematic review rebuts those hypotheses [3]. Nevertheless, there are singular case reports of seasonal clinical exacerbation and histological aggravation of an otherwise well controlled EoE, due to significant exposure to airborne allergens.

In spite of the growing use of SLIT for environmental and food allergy, it has been exceptionally related to EoE, with 7 cases published in the literature so far (Table 1). The first case of a 44-year-old female that developed dysphagia 4 weeks after initiation of a hazelnut/birch alder/oak pollen sublingual extract was brought by Miehlke in 2013 [4]. Afterwards, two cases were described following the start of SLIT with dust mites [5, 6], two triggered by grass pollen [7, 8] and one by a cedar pollen extract [9]. The most recent case was reported in a 38-year-old female after 3-year maintenance of SLIT with a latex extract [10]. Six out of this 7 patients initiated esophageal symptoms within less than 6 weeks from the beginning of the immunotherapy. In all patients the SLIT extract was discontinued. The only one case in which SLIT was switched to SCIT, resulted in a relapse of esophageal symptoms. However, this 10-year-old boy suffered from histologically confirmed EoE before starting immunotherapy, and no new biopsies were performed later, establishing the relation between EoE and SLIT/SCIT merely based on clinical symptoms [8].

We present a case of a female with chronic gastritis that portrays the development of EoE due to SLIT with a grass pollen extract. The chronology of symptoms´ emergence, histological confirmation, and the remission of symptoms and inflammation after SLIT discontinuation

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advocate for a cause-effect relationship. Additionally, long follow-up period of more than five years supports our conclusions.

Furthermore, we demonstrate the tolerance to a subcutaneous pollen extract, suggesting that direct contact of the allergen with esophageal mucosa may be mandatory to develop EoE. This fact, to our knowledge, has not been previously described in the literature.

Although extremely uncommon, EoE can constitute an unwanted side-effect of SLIT. Herein the allergist must be alert in order to detect characteristic symptoms to discontinue the therapy and to provide proper care for the patient. Continuation of the specific immunotherapy may be feasible by changing the way of administration (SCIT), always under close clinical and endoscopic monitoring. More clinical investigation of these cases is needed for a full understanding of this phenomenon.

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Conflicts of interest

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Table 1. Cases reported in the literature of SLIT-induced eosinophilic esophagitis. eos/hpf: eosinophils per high power field; PPI: proton pump inhibitors; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy.

Authors	**Sex age (y)**	**Allergen extract**	**Time to symptoms onset**	**Endoscopic findings**	**Biopsy findings**	**Intervention**	**Outcome**
Miehlke *et al.* 2013 [5]	female 44	hazelnut, birch, alder	8 weeks	whitish exudates longitudinal furrows	164 eos/ hpf	discontinued SLIT	negative biopsy at 4 weeks
Antico *et al.* 2014 [8]	male 23	timothy grass	4 weeks	Not found	18-24 eos/hpf	discontinued SLIT	negative biopsy at 3 months
Béné *et al.* 2016 [6]	female 10	dust mite	6 weeks	focal congestion of gastric mucosa	100 eos/hpf,	discontinued SLIT, PPIs	negative biopsy at 4 weeks
Rokosz *et al.* 2017 [7]	male 9	grass, tree, dust mite	13 months	not mentioned	57 eos/hpf	discontinued SLIT, PPIs	negative biopsy at 12 months
Kawashima *et al.* 2018 [10]	male 53	cedar	18 days	linear furrows, concentric rings, whitish exudates	61 eos/hpf	discontinued SLIT, PPIs	negative biopsy at 8 weeks
Wells *et al.* 2018 [9]	male 10	five grass mix	10 months	not mentioned	not mentioned	discontinued SLIT, PPIs, budesonide slurry	clinical resolution No biopsy **Recurrence with SCIT**
Nucera *et al.* 2020 [11]	female 38	latex	3 years	circular rings, linear furrows, whitish exudates	25 eos/hpf	discontinued SLIT, PPIs	negative biopsy at 12 weeks

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